## REMARKS AND ARGUMENTS

Claims 1-30 are presently pending in the application. Claims 1, 5-7, 13, 17-21 and 25-27 are amended and claims 4, 16 and 24 are canceled without any prejudice or disclaimer of any previously claimed subject matter. Applicant reserves the right to prosecute any cancelled subject matter in a divisional or continuation application.

**Rejections under 35 U.S.C. § 112**

The Examiner has rejected the specification and original claims 1-3, 7-15, 19-23, 27 and 28-30 under 35 U.S.C. § 112, first paragraph as not providing sufficient written description for a skilled artisan to identify compounds with inosine monophosphate dehydrogenase inhibition activity without undue experimentation. Solely to promote prosecution, the Applicants have limited the claims to recite combinations of β-D-1,3-dioxolanyl purines with mycophenolic acid or ribavirin, or a pharmaceutically acceptable ester or salt thereof, which find support throughout the specification, for example on pages 13, 17 and 25, and are exemplified in the specification on pages 28-41. It is submitted that these amendments overcome the Examiner's rejection.

The Examiner has also rejected claims 28-29 under 35 U.S.C. § 112, second paragraph because the term "enantiomerically enriched" is considered indefinite because the Examiner contends that there is no criteria defining this term in the specification. Contrary to the Examiner's assertion, the specification does define the term "enantiomerically enriched." Specifically, the term is defined on page 15 as "approximately 95% or greater, preferably at least 96%, more preferably at least 97%, even more preferably at least 98%, and even more preferably at least about 99% or more of a single enantiomer" (see lines 21-24). The term thus does not include almost any compound, but only includes those that are found predominantly in the form of a single enantiomer, as defined on page 15.

**Rejections under 35 U.S.C. § 103**

Claims 1-30 were rejected under 35 U.S.C. §103, because they are allegedly unpatentable over ICHIMURA et al. "Polymerase Substrate Depletion: A Novel Strategy for Inhibiting the Replication of the Human Immunodeficiency Virus" Virology, **1995**, *211* (2), 554-560; FERNANDEZ-LARSSON et al. "Ribavirin is an Inhibitor of Human Immunodeficiency Virus Reverse Transcriptase" Molecular Pharmacology, **1990**, *38* (2), 766-770; and BELLEAU et al., U.S. Patent No. 5,270,315. The basis for the Examiner's rejection is that mycophenolic acid, ribavirin, and DXG/DAPD are compounds with known anti-HIV activity, as set forth by ICHIMURA, FERNANDEZ-LARSSON and BELLEAU, and that the skilled artisan would therefore be motivated to combine these compounds with DAPD for the treatment of HIV.

Contrary to the Examiner's assertion, while it is known that combination therapies can be helpful in the treatment of HIV, it is not known which drug combinations will be efficacious and/or synergistic rather than antagonistic or simply additive. The Applicants have *unexpectedly* found that the combination of mycophenolic acid or ribavirin with a β-D-1,3-dioxolanyl purine provides synergistic anti-HIV effects. The Applicants also unexpectedly found that the combination of mycophenolic acid or ribavirin with a β-D-1,3-dioxolanyl purine has beneficial effects against drug-resistant HIV, such as DAPD and/or DXG resistant HIV.

Biological data pertaining to the discovery that the combination of mycophenolic acid or ribavirin with a β-D-1,3-dioxolanyl purine exhibit synergistic effects is described in the specification. For example, on pages 30-31, combination assays are described in which $EC_{50}$ values for DAPD, DXG, Abacavir and AZT were determined in the presence or absence of 1, 5, 10 and 20 μM ribavirin (RBV) in the MT2 cell line (see Table 2, page 31). Table 3 on page 31 of the specification illustrates the fold differences in $EC_{50}$ values obtained for each of the compounds in combination with ribavirin. Combination with ribavirin **decreased** the $EC_{50}$ for DAPD and DXG more than ten-fold at 20μM, while combination with Abacavir had **no effect** (less than 2 fold difference in the apparent $EC_{50}$) and **increased** the apparent $EC_{50}$ of AZT more than six-fold. Similar results were obtained in PBM cells (Tables 5-6, page 33).

Combination assays were also performed to determine $EC_{50}$ values for DAPD, DXG, Abacavir, AZT and FTC, alone or with 0.25, 0.1, and 0.01 μM of mycophenolic acid (MPA) in MT2 cells (see Table 8, page 37). In the MT2 cell line, mycophenolic acid was not even active against HIV replication, however addition of 0.25 μM mycophenolic acid produced a 16.7 and 10.5 fold **decrease** in the apparent $EC_{50}$ values of DAPD and DXG, respectively. Table 9 on pages 37-38 of the specification illustrates the fold differences in $EC_{50}$ values obtained for each of the compounds in combination with 0.1 and 0.25 μM mycophenolic acid. In contrast to DAPD or DXG, addition of 0.25 μM mycophenolic acid produced less than a 2 fold decrease in the apparent $EC_{50}$ of Abacavir and FTC, and resulted in a 2.3 fold **increase** in the apparent $EC_{50}$ of AZT indicating that the combination is antagonistic. Similar results were obtained in PBM cells (see Tables 11-12, pages 39-40).

Furthermore, the specification includes biological data regarding the unexpected discovery that the combination of mycophenolic acid or ribavirin with a β-D-1,3-dioxolanyl purine exhibit synergistic effects in drug-resistant variants of HIV. For example, on page 32, the effect of ribavirin (RBV) on the activity of DAPD and DXG against mutant strains of HIV was analyzed (see Table 4). The mutant viruses tested all demonstrated increased $EC_{50}$ values (greater than four fold) for both DAPD and DXG indicating resistance to these compounds. Addition of 20 μM ribavirin *decreased* the $EC_{50}$ values of DAPD and DXG against these viruses. The $EC_{50}$ values determined for DAPD and DXG in the presence of 20 μM ribavirin were at least 2.5-fold lower than those obtained for the wild type virus (see Table 4). On pages 38-39, the effect of mycophenolic acid (MPA) on the activity of DAPD and DXG against mutant strains of HIV was also analyzed (see Table 10). Addition of 0.25 μM mycophenolic acid also decreased the $EC_{50}$ values of DAPD and DXG against the mutant viruses, indicating that mycophenolic acid compensates for the resistance to DAPD and DXG.

Therefore, both ribavirin and mycophenolic acid, when combined with DAPD or DXG provide an unexpected synergistic anti-HIV response against wild-type virus. When tested against wild-type virus, using either human PBMC or MT2 cells, both mycophenolic acid (MPA) and ribavirin (RBV) decreased the $EC_{50}$ value for DXG by at least 10-fold. In contrast, both mycophenolic acid and ribavirin increase the $EC_{50}$ value for AZT and had little or no effect on

the activity of abacavir or FTC when tested in the MT2 cell line. These results could not have been predicted from the disclosure of the use of the individual compounds in the cited art.

In light of the claim amendments and arguments presented, the Examiner's objections to dependent claims 8-12 as merely citing additional methods of administration are rendered moot.

In view of the present amendment and response to Office action, Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

No fee is believed to be required for this Response to Office Action, however the Commissioner is authorized to charge any required fees to Deposit Account 11-0980.

Respectfully submitted,

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